NATIONAL GUIDELINE CLEARINGHOUSE™ (NGC)
GUIDELINE SYNTHESIS

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PART II. DIAGNOSIS AND MANAGEMENT OF ACUTE EXACERBATIONS

GUIDELINES

1. American College of Physicians/American College of Chest Physicians (ACP/ACCP). Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 2001 Apr 3;134(7):595-9 [3 references].
2. *Finnish Medical Society Duodecim. Chronic obstructive pulmonary disease (COPD). In: EBM Guidelines. Evidence-Based Medicine [CD-ROM]. Helsinki, Finland: Duodecim Medical Publications Ltd.; 2005 Mar 2 [various]. [37 references]
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, 2005. 115 p.
4. National Collaborating Centre for Chronic Conditions, National Institute for Health and Clinical Excellence (NCCCC/NICE). Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004 Feb;59 Suppl 1:1-232. [491 references]

*Note: This guideline summary has been updated. NGC is working to update this synthesis.

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INTRODUCTION

A direct comparison of the American College of Physicians (formerly the American College of Physicians-American Society of Internal Medicine)/American College of Chest Physicians (ACP/ACCP), the Finnish Medical Society Duodecim (Finnish), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization and the National Heart, Lung, and Blood Institute), and the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]) recommendations for the diagnosis and management of acute exacerbation of chronic obstructive pulmonary disease (COPD) is provided in the tables below. The Finnish, GOLD, and NCCCC/NICE guidelines are broad in scope, providing recommendations on diagnosis and management of both stable and acute exacerbations of COPD; the GOLD guideline also addresses prevention strategies. The ACP/ACCP guideline focuses only on diagnosis and management of acute exacerbation of COPD in the inpatient setting and does not provide recommendations for patients with stable disease. Recommendations concerning diagnosis and management of stable COPD are compared in Part I of this synthesis. Recommendations for pulmonary rehabilitation of patients with COPD are addressed in Part III of this synthesis (currently under development).

Table 1 gives a broad overview of the four guidelines. Table 2 details the recommendations for diagnosis and management of acute exacerbations of COPD. Benefits and harms that relate to the major recommendations are listed in Table 3. The supporting evidence is classified and identified with selected major recommendations for Finnish, GOLD, and NCCCC/NICE. The definitions of their rating schemes are included in Table 4. Although ACP/ACCP does not specifically state the type of supporting evidence for individual recommendations, their guideline considered the best available evidence for each subtopic selected for analysis.

Following the content and recommendation comparison tables, the areas of agreement and differences among the guidelines are identified. The evidence surrounding disparate recommendations is explored in the discussion of areas of difference.

Abbreviations:

- ACCP, American College of Chest Physicians
- ACP, American College of Physicians
- COPD, Chronic obstructive pulmonary disease
- ECG, Electrocardiogram
- Finnish, Finnish Medical Society Duodecim
- FEV_1, Forced expiratory volume in one second
- GOLD, Global Initiative for Chronic Obstructive Lung Disease
- ICU, Intensive Care Unit
- NCCCC, National Collaborating Centre for Chronic Conditions
- NICE, National Institute for Health and Clinical Excellence
- NIPPV, Noninvasive positive pressure ventilation
- PEF, Peak expiratory flow

TABLE 1: COMPARISON OF SCOPE AND CONTENT	
Objective and Scope	
ACP/ACCP (2001)	• To present evidence-based recommendations for the diagnostic evaluation, risk stratification, and therapeutic management of patients with acute exacerbations of COPD
Finnish (2004)	• Evidence-Based Medicine Guidelines collect, summarize, and update the core clinical knowledge essential in general practice. The guidelines also describe the scientific evidence underlying the given recommendations.
GOLD (2005)	• To recommend effective COPD management and prevention strategies for use in all countries • To increase awareness of the medical community, public health officials, and the general public that COPD is a public health problem • To decrease morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management • To improve prevention and management of COPD through implementation and evaluation of effective programs for diagnosis and management • To encourage renewed research interest in this highly prevalent disease
NCCCC/NICE (2004)	• To develop a clinical guideline on the management of chronic obstructive pulmonary disease for use in the National Health Service (NHS) in England and Wales • To offer best practice advice on the identification and care of patients with COPD

	• To define the symptoms, signs, and investigations required to establish a diagnosis of COPD • To define the factors that are necessary to assess the severity of COPD, provide prognostic information, and guide best management • To provide guidance on the pharmacological and non-pharmacological treatment of patients with stable COPD and on the management of exacerbations • To discuss the interface with surgery and intensive therapy units
Target Population	
ACP / ACCP (2001)	• Patients with acute exacerbations of COPD in the emergency department or inpatient setting Note: Patients with stable COPD were not considered.
Finnish (2004)	• Finland • Adults with COPD Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning stable COPD are provided in Part I of this synthesis
GOLD (2005)	• Individuals with COPD Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning stable COPD are provided in Part I of this synthesis
NCCCC / NICE (2004)	• England and Wales • Adults who have a clinical working diagnosis of COPD, including chronic bronchitis, emphysema, and chronic airflow limitation/obstruction Note: The guideline does not cover the management of people with asthma, bronchopulmonary dysplasia, and bronchiectasis, nor does it cover children. Note: This guideline includes recommendations for patients with both chronic stable disease and patients with acute exacerbations of COPD. Recommendations concerning stable COPD are provided in Part I of this synthesis
Intended Users	
ACP / ACCP (2001)	Nurses Physician Assistants

	Physicians Respiratory Care Practitioners
Finnish (2004)	Health Care Providers Physicians
GOLD (2005)	Advanced Practice Nurses Allied Health Personnel Nurses Physician Assistants Physicians Public Health Departments Respiratory Care Practitioners
NCCCC/NICE (2004)	Advanced Practice Nurses Allied Health Personnel Dietitians Health Care Providers Hospitals Nurses Occupational Therapists Patients Physical Therapists Physicians Public Health Departments Respiratory Care Practitioners Students

Interventions And Practices Considered	
ACP / ACCP (2001)	Diagnosis / Assessment 1. Identification of signs and symptoms 2. Causes of exacerbation 3. Assessing severity of exacerbation 4. Spirometry 5. Chest x-ray 6. Further investigations such as pulse oximetry, sputum smear, and culture were not considered Management / Treatment 1. Pharmacologic therapy, including: • Bronchodilators (short-acting and long-acting beta$_2$-agonist and/or anticholinergics) • Theophylline • Corticosteroid therapy • Combination therapy • Antibiotics 2. Oxygen therapy 3. Noninvasive positive-pressure ventilation 4. Invasive mechanical ventilation
Finnish (2004)	Diagnosis / Assessment 1. Identification of signs and symptoms 2. Assessing severity of exacerbation Management / Treatment 1. Home vs. inpatient management 2. Pharmacologic therapy, including: • Bronchodilators (short-acting and long-acting beta$_2$-agonist and/or anticholinergics) • Theophylline • Corticosteroid therapy • Combination therapy • Antibiotics 3. Oxygen therapy 4. Noninvasive positive-pressure ventilation 5. Invasive mechanical ventilation Note: For specific interventions concerning diagnosis and management of chronic COPD, see Part I of this synthesis. For interventions on pulmonary rehabilitation, see Part III of this synthesis (under development).

GOLD (2005)	Diagnosis/Assessment 1. Identification of signs and symptoms 2. Causes of exacerbation 3. Assessing severity of exacerbation 4. Spirometry 5. Chest x-ray 6. Further investigations, as needed, including pulse oximetry, sputum smear, and culture, ECG, etc. Management/Treatment 1. Home vs. inpatient management 2. Pharmacologic therapy, including: • Bronchodilators (short-acting and long-acting beta$_2$-agonist and/or anticholinergics) • Theophylline • Corticosteroid therapy • Combination therapy • Antibiotics 3. Oxygen therapy 4. Noninvasive positive-pressure ventilation 5. Invasive mechanical ventilation 6. Discharge planning and follow up/monitoring Note: For specific interventions concerning diagnosis and management of chronic COPD, see Part I of this synthesis. For interventions on pulmonary rehabilitation, see Part III of this synthesis (under development).
NCCCC/NICE (2004)	Diagnosis/Assessment 1. Identification of signs and symptoms 2. Causes of exacerbation 3. Assessing severity of exacerbation 4. Spirometry 5. Chest x-ray 6. Further investigations, including pulse oximetry, sputum smear, and culture, ECG, full blood count, urea and electrolyte concentrations, theophylline level, etc. Management/Treatment 1. Home vs. inpatient management 2. Pharmacologic therapy, including: • Bronchodilators (short-acting and long-acting beta$_2$-agonist and/or anticholinergics) • Theophylline • Corticosteroid therapy • Combination therapy • Antibiotics 3. Oxygen therapy

	4. Noninvasive positive-pressure ventilation 5. Invasive mechanical ventilation 6. Discharge planning and follow up/monitoring Note: For specific interventions concerning diagnosis and management of chronic COPD, see Part I of this synthesis. For interventions on pulmonary rehabilitation, see Part III of this synthesis (under development).

TABLE 2: COMPARISON OF RECOMMENDATIONS FOR ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)	
DIAGNOSIS AND INITIAL ASSESSMENT	
Signs and Symptoms of Acute Exacerbation	
ACP / ACCP (2001)	There is no widely accepted definition of acute exacerbation of COPD, but most published definitions encompass some combination of three clinical findings: worsening dyspnea, increase in sputum purulence, and increase in sputum volume.
Finnish (2004)	Although not specifically stated in the guideline, factors that indicate the initiation of treatment for the management of an acute infection include: • Increased dyspnoea • Increased sputum • Purulent sputum
GOLD (2005)	Increased breathlessness is the main symptom of an exacerbation, and is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color and/or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, and/or new radiological anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does a prior history of chronic sputum production.
NCCCC / NICE (2004)	Definition An exacerbation is a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations and is acute in onset. Commonly reported symptoms are worsening breathlessness, cough,

	increased sputum production, and change in sputum colour. The change in these symptoms often necessitates a change in medication. Sign and Symptoms Exacerbations of COPD can be associated with the following symptoms: • Increased dyspnoea • Increased sputum purulence • Increased sputum volume • Increased cough • Upper airway symptoms (e.g., colds and sore throats) • Increased wheeze • Chest tightness • Reduced exercise tolerance • Fluid retention • Increased fatigue • Acute confusion Chest pain and fever are uncommon features of COPD exacerbations and should prompt a search for other aetiologies. Differential Diagnosis of an Exacerbation Other conditions may present with similar symptoms in patients with COPD. These must be considered and excluded when making a diagnosis of an exacerbation. Other causes of similar symptoms in patients with COPD are: • Pneumonia • Pneumothorax • Left ventricular failure/pulmonary oedema • Pulmonary embolus • Lung cancer • Upper airway obstruction • Pleural effusion • Recurrent aspiration
Causes of Exacerbation	
ACP / ACCP (2001)	Acute exacerbations can be triggered by tracheobronchial infections or environmental exposures, and patients often have associated clinical conditions, such as heart failure, extrapulmonary infections, and pulmonary embolism.
Finnish	Not addressed in the guideline.

(2004)	
GOLD (2005)	The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified. The role of bacterial infections, once believed to be the main cause of COPD exacerbations, is controversial, but recent investigations with newer research techniques have begun to provide important information. Conditions that may mimic an exacerbation include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia.
NCCCC / NICE (2004)	A number of factors are known to cause exacerbations of COPD. Although bacteria can be cultured from the sputum of patients with stable COPD there is evidence that they are also responsible for exacerbations. Viruses are also important aetiological agents, particularly during winter months. Non-infectious agents are also responsible for some exacerbations. The following factors are known causes of exacerbations of COPD: 1. Infections • Rhinoviruses (common cold) • Influenza • Parainfluenza • Coronavirus • Adenovirus • Respiratory syncytial virus • Chlamydia pneumoniae • Haemophilus influenzae • Streptococcus pneumoniae • Moraxella catarrhalis • Staphylococcus aureus • Pseudomonas aeruginosa 2. Common pollutants • Nitrogen dioxide • Particulates • Sulphur dioxide • Ozone The cause of the exacerbation may be unidentifiable in up to 30% of exacerbations.
Assessing Severity of Exacerbation	
ACP / ACCP (2001)	Unlike the staging system for stable COPD, there are no standardized, validated grading systems for severity of an acute exacerbation. Probably the most commonly used system is that developed by Anthonisen and colleagues. In this system, patients

	with type 1 exacerbation (severe) have all three cardinal symptoms of acute exacerbation: worsening of dyspnea, increase in sputum purulence, and increase in sputum volume. Patients with type 2 exacerbation (moderate) exhibit two of the cardinal symptoms. Type 3 exacerbations (mild) have one of these clinical findings plus at least one of the following: an upper respiratory tract infection in the past 5 days, fever without other apparent cause, increased wheezing, increased cough, or a 20% increase in respiratory rate or heart rate above baseline.
Finnish (2004)	Not addressed in the guideline
GOLD (2005)	Assessment of the severity of an acute exacerbation is based on the patient's medical history before the exacerbation, symptoms, physical examination, lung function tests, arterial blood gas measurements, and other laboratory tests. The medical history should cover how long worsening or new symptoms have been present, the frequency and severity of breathlessness and coughing attacks, sputum volume and color, limitation of daily activities, and previous episodes/exacerbations and whether they required hospitalization, and the present treatment regimen. When available, prior measurements of lung function and arterial blood gases are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. In patients with very severe COPD, the most important sign of severe exacerbation is a change in alertness of the patient and this signals a need for immediate evaluation in the hospital.
NCCCC/NICE (2004)	Some exacerbations are mild and self-limiting. These are frequently managed by patients at home without consulting healthcare professionals. Other exacerbations are severe, carry a risk of death, and require hospitalisation. A number of factors can be used to assess the severity of an exacerbation. Not all will be present, but the occurrence of any of these should alert the clinician. The following signs are features of a severe exacerbation: • Marked dyspnoea • Tachypnoea • Purse lip breathing • Use of accessory muscles (sternomastoid and abdominal) at rest • Acute confusion • New onset cyanosis • New onset peripheral oedema • Marked reduction in activities of daily living

Diagnostic Testing	
ACP / ACCP (2001)	Lung Function / Spirometry For patients hospitalized with an acute exacerbation of COPD, acute spirometry should not be used to diagnose an exacerbation or to assess its severity. Arterial Blood Gases Indirect evidence shows that arterial blood gases are helpful for determining the present need for oxygen therapy and the potential need for mechanical ventilatory support. Chest Radiograph An admission chest radiography may be useful since it has been shown that up to 23% of patients admitted had changes in management related to findings on chest radiography. Chest radiography in patients visiting the emergency department may also useful. To date, there is no evidence for or against the utility of chest radiography in the office setting. Other Laboratory Tests The developers did not find enough evidence to make recommendations regarding the use of pulse oximetry, sputum smear, and culture.
Finnish (2004)	Not addressed in the guideline
GOLD (2005)	When available, prior measurements of lung function and arterial blood gases are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. Lung Function / Spirometry Even simple lung function tests can be difficult for a sick patient to perform properly. In general, a PEF <100 L per minute or an FEV_1 <1.00 L indicates a severe exacerbation. Arterial Blood Gases In the hospital, measurement of arterial blood gases is essential to assess the severity of an exacerbation. A PaO_2 <8.0 kPa (60 millimeters Hg) and/or SaO_2 <90% with or without $PaCO_2$ >6.7 kPa, 50 mmHg (when breathing room air) indicates respiratory

	failure. In addition, PaO_2 <6.7 kPa (50 millimeters Hg), $PaCO_2$ >9.3 kPa (70 mm Hg), and pH <7.30 point towards a life-threatening episode that needs close monitoring or critical management Chest X-ray and ECG Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. Although the history and physical signs can be confusing, especially when pulmonary hyperinflation masks coexisting cardiac signs, most problems are resolved by the chest x-ray and ECG. An ECG aids in the diagnosis of right heart hypertrophy, arrhythmias, and ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an acute exacerbation, especially in severe COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing ECG and radiographic results. Spiral computed tomography (CT) scanning and angiography, and perhaps specific D-dimer assays, are the best tools presently available for the diagnosis of pulmonary embolism in patients with COPD, but ventilation-perfusion scanning is of no value. A low systolic blood pressure and an inability to increase the PaO_2 above 8.0 kPa (60 mm Hg) despite high-flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation. Other Laboratory Tests The whole blood count may identify polycythemia (hematocrit >55%) or bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting antibiotic treatment. Streptococcus pneumoniae, Hemophilus influenzae, and Moraxella catarrhalis are the most common bacterial pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Biochemical tests can reveal whether the cause of the exacerbation is an electrolyte disturbance(s) (hyponatremia, hypokalemia, etc.), a diabetic crisis, or poor nutrition (low proteins), and may suggest a metabolic acid-base disorder.
NCCCC/NICE (2004)	The diagnosis of an exacerbation is made clinically and does not depend on the results of investigations; however, in certain situations, investigations may assist in ensuring appropriate treatment is given. Different investigation strategies are required for patients managed in hospital (who will tend to have more severe exacerbations) and those managed in the community.

	Changes in lung function at the time of an exacerbation are usually small and are not helpful in routine practice. Patients may present for the first time with an exacerbation of COPD. In this situation patients need assessing and their diagnosis confirmed as described in section 6 of the original guideline, Diagnosing COPD (see also Part I of this synthesis). Sending sputum samples for culture in primary care is of very limited value because empirical therapy is effective and should be prescribed promptly if the sputum is purulent. D - Recommendations for Primary Care In patients with an exacerbation managed in primary care: • Sending sputum samples for culture is not recommended in routine practice. • Pulse oximetry is of value if there are clinical features of a severe exacerbation. D - Recommendations for Patients Referred to Hospital In all patients with an exacerbation referred to hospital: • A chest radiograph should be obtained. • Arterial blood gas tensions should be measured and the inspired oxygen concentration must be recorded. • An ECG should be recorded (to exclude comorbidities). • A full blood count should be performed and urea and electrolyte concentrations should be measured. • A theophylline level should be measured in patients on theophylline therapy at admission. • If sputum is purulent, a sample should be sent for microscopy and culture. • Blood cultures should be taken if the patient is pyrexial.
MANAGEMENT OF ACUTE EXACERBATIONS	
Outpatient/Home Management vs. Inpatient Management	
ACP/ACCP (2001)	No recommendations offered. Note: This guideline considers only inpatient management.
Finnish (2004)	Hospital at home with support from specialized nurses is a safe alternative for about one in four selected patients with acute exacerbation of COPD (A).

GOLD (2005)	Home Management There is increasing interest in home care for end-stage COPD patients, although economic studies of home care services have yielded mixed results. Four randomized clinical trials have shown nurse-administered home care represents an effective and practical alternative to hospitalization in selected patients with exacerbations of COPD without acidotic respiratory failure. However, the exact criteria for home vs. hospital treatment remains uncertain and will vary by health care setting. A major outstanding issue is when to treat an exacerbation at home and when to hospitalize the patient. Hospital Management The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support. Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Indications for hospital assessment or admission for exacerbations of COPD, include: • Marked increase in intensity of symptoms, such as sudden development of resting dyspnea • Severe background COPD • Onset of new physical signs (e.g., cyanosis, peripheral edema) • Failure of exacerbation to respond to initial medical management • Significant comorbidities • Newly occurring arrhythmias • Diagnostic uncertainty • Older age • Insufficient home support Indications for ICU admission of patients with exacerbations of COPD, include: • Severe dyspnea that responds inadequately to initial emergency therapy • Confusion, lethargy, coma • Persistent or worsening hypoxemia (PaO_2 <5.3 kPa, 40 mm Hg), and/or severe/worsening hypercapnia ($PaCO_2$ >8.0 kPa, 60 mm Hg), and/or severe/worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and NIPPV Admission of patients with severe COPD exacerbations to

	intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment are available to identify and manage acute respiratory failure successfully.
NCCCC/NICE (2004)	D - Factors that should be considered when deciding whether to treat the patient in the home or in a hospital are listed below: Treat at Home • Able to cope at home - Yes • Breathlessness - Mild • General condition - Good • Level of activity - Good • Cyanosis - No • Worsening peripheral oedema - No • Level of consciousness - Normal • Already receiving long-term oxygen therapy (LTOT) - No • Social circumstances - Good • Acute confusion - No • Rapid rate of onset - No • Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes) - No • SaO_2 <90% - No • Changes on the chest radiograph - No • Arterial pH level - $\geq$7.35 • Arterial PaO_2 - $\geq$7 kPa Treat in Hospital 1. Able to cope at home - No 2. Breathlessness - Severe 3. General condition - Poor/deteriorating 4. Level of activity - Poor/confined to bed 5. Cyanosis - Yes 6. Worsening peripheral oedema - Yes 7. Level of consciousness - Impaired 8. Already receiving long-term oxygen therapy (LTOT) - Yes 9. Social circumstances - Living alone/not coping 10. Acute confusion - Yes 11. Rapid rate of onset - Yes 12. Significant comorbidity (particularly cardiac disease and insulin-dependent diabetes) - Yes 13. Changes on the chest radiograph - Present 14. Arterial pH level - $\geq$7.35 15. Arterial PaO_2 - $\leq$7 kPa A - Hospital-at-home and assisted-discharge schemes are safe and effective and should be used as an alternative way of managing patients with exacerbations of COPD who would

	otherwise need to be admitted or stay in hospital. D - The multi-professional team required to operate these schemes should include allied heath professionals with experience in managing patients with COPD, and may include nurses, physiotherapists, occupational therapists, and generic health workers. D - There are currently insufficient data to make firm recommendations about which patients with an exacerbation are most suitable for hospital-at-home or early discharge. Patient selection should depend on the resources available and absence of factors associated with a worse prognosis, such as acidosis. D - Patient's preferences about treatment at home or in hospital should be considered.
PHARMACOLOGIC TREATMENT	
Bronchodilators (Including Delivery Systems)	
ACP / ACCP (2001)	Inhaled anticholinergic bronchodilators or inhaled short-acting beta$_2$ agonists are beneficial in the treatment of patients presenting to the hospital with acute exacerbation of COPD. Since the inhaled anticholinergic bronchodilators have fewer and more benign side effects, consider these agents first. Only after the initial bronchodilator is at maximum dose is the addition of a second inhaled bronchodilator beneficial. Some evidence shows that the efficacy of wet nebulization and dry aerosol delivery systems (metered-dose inhaler plus a spacer) are clinically equivalent. Therefore, the choice of a specific delivery method should be determined on an individual basis, depending on each patient's ability to use the different methods. In the treatment of patients with acute exacerbation of COPD, the following therapeutic options are not beneficial: mucolytic medications, chest physiotherapy, and methylxanthine bronchodilators. The latter two options may be harmful.
Finnish (2004)	An inhaled sympathomimetic (salbutamol 2.5-5 milligrams or terbutaline 5-10 milligrams) by a dosing device or a spray. Inhaled ipratropium bromide 0.5 mg can be added to it. There is no evidence of a significant effect of theophylline infusion (C) and its usage is not recommended. It may sometimes be used at a dose of 0.5 mg/kg/h if response to other treatments is poor. Serum theophylline concentration should be monitored if possible.

GOLD (2005)	Home Management Home management of COPD exacerbations involves increasing the dose and/or frequency of existing bronchodilator therapy (Evidence A). If not already used, an anticholinergic can be added until the symptoms improve. In more severe cases, high-dose nebulizer therapy can be given on an as-needed basis for several days and if a suitable nebulizer is available. However, long-term use of nebulizer therapy after an acute episode is not routinely recommended. Hospital Management Short-acting inhaled $beta_2$-agonists are usually the preferred bronchodilators for treatment of exacerbations of COPD (Evidence A). If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is controversial. Despite its wide-spread clinical use, the role of aminophylline in the treatment of exacerbations of COPD remains controversial. Most studies of aminophylline have demonstrated minor improvements in lung volumes without showing gas exchange deterioration. In more severe exacerbations, addition of an oral or intravenous methylxanthine to the treatment can be considered. However, close monitoring of serum theophylline is recommended to avoid the side effects of these drugs. Possible beneficial effects in lung function, and clinical endpoints, are modest and inconsistent, whereas adverse effects are significantly increased. Additional considerations regarding bronchodilators in the management of severe or life-threatening exacerbations of COPD in the emergency department or the hospital: • Increase doses or frequency • Combine $beta_2$-agonists and anticholinergics • Use spacers or air-driven nebulizers • Consider adding intravenous aminophylline, if needed
NCCCC/NICE (2004)	Increased breathlessness is a common feature of an exacerbation of COPD. This is usually managed by taking increased doses of short-acting bronchodilators. As well as taking increased doses of bronchodilators at the time of an exacerbation, these drugs may be given using different delivery systems. Note: The guideline does not offer recommendations specific to the use of $beta_2$ agonists in acute exacerbation. Delivery Systems for Inhaled Therapy During

	Exacerbations A - Both nebulisers and hand-held inhalers can be used to administer inhaled therapy during exacerbations of COPD. D - The choice of delivery system should reflect the dose of drug required, the ability of the patient to use the device, and the resources available to supervise the administration of the therapy. D - Patients should be changed to hand-held inhalers as soon as their condition has stabilised because this may permit earlier discharge from hospital. D - If a patient is hypercapnic or acidotic, the nebuliser should be driven by compressed air, not oxygen (to avoid worsening hypercapnia). If oxygen therapy is needed, it should be administered simultaneously by nasal cannulae. D - The driving gas for nebulised therapy should always be specified in the prescription. Theophylline and Other Methylxanthines D - Intravenous theophylline should only be used as an adjunct to the management of exacerbations of COPD if there is an inadequate response to nebulised bronchodilators. D - Care should be taken when using intravenous theophylline because of interactions with other drugs and potential toxicity if the patient has been on oral theophylline. D - Theophylline levels should be monitored within 24 hours of starting treatment and subsequently as frequently as indicated by the clinical circumstances.
Combination Therapy	
ACP / ACCP (2001)	Only after the initial bronchodilator is at maximum dose is the addition of a second inhaled bronchodilator beneficial.
Finnish (2004)	An inhaled sympathomimetic (salbutamol 2.5-5 mg or terbutaline 5-10 mg) by a dosing device or a spray can be combined with an inhaled ipratropium bromide 0.5 mg.
GOLD (2005)	If a prompt response to beta$_2$ agonists does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is rather controversial.

NCCCC / NICE (2004)	The guideline does not offer specific recommendations regarding combination therapy with inhaled anticholinergics and short-acting beta$_2$-agonists in an acute exacerbation of COPD.
Corticosteroids	
ACP / ACCP (2001)	In the treatment of patients presenting to the hospital with moderate or severe acute exacerbation of COPD, systemic corticosteroids given for up to 2 weeks are beneficial in patients who are not receiving long-term therapy with oral steroids. Inhaled steroids are not appropriate in the treatment of acute exacerbation of COPD.
Finnish (2004)	Methyl prednisolone 0.5 mg/kg every 6 hours is probably beneficial. Also oral corticosteroids (prednisolone 30-40 mg/day) are used empirically for 7 to 14 days.
GOLD (2005)	Home Management Systemic glucocorticosteroids are beneficial in the management of acute exacerbations of COPD. They shorten recovery time and help to restore lung function more quickly (Evidence A). They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is less than 50% predicted. A dose of 40 mg of prednisolone per day for 10 days is recommended (Evidence D). One large study indicates that nebulized budesonide may be an alternative to oral glucocorticosteroids in the treatment of nonacidotic exacerbations. Hospital Management Oral or intravenous glucocorticosteroids are recommended as an addition to bronchodilator therapy (plus eventually antibiotics and oxygen therapy) in the hospital management of acute exacerbations of COPD (Evidence A). The exact dose that should be given is not known, but high doses are associated with a significant risk of side effects. 30 to 40 mg of oral prednisolone daily for 10 to 14 days is a reasonable compromise between efficacy and safety (Evidence D). Prolonged treatment does not result in a greater efficacy and increases the risk of side effects.
NCCCC / NICE (2004)	A - In the absence of significant contraindications, oral corticosteroids should be used, in conjunction with other therapies, in all patients admitted to hospital with an exacerbation of COPD. B - In the absence of significant contraindications, oral corticosteroids should be considered in patients managed in the community who have an exacerbation with a significant increase

	in breathlessness which interferes with daily activities. D - Patients requiring corticosteroid therapy should be encouraged to present early to get maximum benefits. D - Prednisolone 30 mg orally should be prescribed for 7 to 14 days. A - It is recommended that a course of corticosteroids treatment should not be longer than 14 days as there is no advantage in prolonged therapy. D - For guidance on stopping oral corticosteroid therapy it is recommended that clinicians refer to the British National Formulary. D - Osteoporosis prophylaxis should be considered in patients requiring frequent courses of oral corticosteroids. D - Patients should be made aware of the optimum duration of treatment and the adverse effects of prolonged therapy. D - Patients, particularly those discharged from hospital, should be given clear instructions about why, when, and how to stop their corticosteroid treatment.
Antibiotics	
ACP / ACCP (2001)	In patients with severe exacerbations of COPD, initial narrow-spectrum antibiotics are reasonable first-line agents. The superiority of newer, more broad-spectrum antibiotics has not been established. Randomized, placebo-controlled trials favored amoxicillin, trimethoprim-sulfamethoxazole, and tetracycline. Most of these studies were done before the emergence of multidrug-resistant organisms, particularly Streptococcus pneumoniae. To date, however, no randomized, placebo-controlled trials have proved the superiority of newer broad-spectrum antibiotics in acute exacerbations of COPD. The trials also did not include nursing home residents or recently hospitalized patients.

Finnish (2004)	• Antimicrobial treatment in exacerbation of COPD is controversial (B). Factors that indicate starting antimicrobial treatment include:
	  • Increased dyspnoea
	  • Increased sputum
	  • Purulent sputum
	• If the patient exhibits two of the three symptoms listed above, an antimicrobial drug is usually indicated (B).

	• Alternatives in antimicrobial treatment:
	  • Amoxicillin 500 mg three times daily for 10 days
	  • Doxycycline 150 mg once daily for 10 days
	  • Sulpha-trimethoprim, dose of trimethoprim 160 mg twice daily for 10 days
	• Antibiotics do not belong to the basic maintenance therapy of COPD.

GOLD (2005)	Randomised placebo controlled studies of antibiotic treatment in exacerbations of COPD have demonstrated a small beneficial effect of antibiotics on lung function, and one randomised controlled trial has provided evidence for a significant beneficial effect of antibiotics in COPD patients who presented with an increase in all three of the following cardinal symptoms: dyspnea, sputum volume, sputum purulence. There was also some benefit in those patients with an increase in only two of these cardinal symptoms. A study on non-hospitalized patients with exacerbations of COPD showed a relationship between the purulence of the sputum and the presence of bacteria, suggesting that these patients should be treated with antibiotics if they also have at least one of the other two cardinal symptoms (dyspnea or sputum volume). However, these criteria for exacerbations of COPD have not been validated in other studies. A study in COPD patients with exacerbations requiring mechanical ventilation (invasive and non-invasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary intra-hospital pneumonia. Based on the current available evidence, antibiotics should be given to: • Patients with exacerbations of COPD with three of the following cardinal symptoms: increased dyspnea, increased sputum volume, increased sputum purulence (Evidence B) • Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (Evidence C) Patients with a severe exacerbation of COPD that requires invasive mechanical ventilation (invasive and non-invasive) (Evidence B) The predominant bacterial organisms recovered in the lower airways of patients with mild exacerbations are Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. In contrast, studies in patients requiring mechanical ventilation with severe underlying COPD have shown that other

	microorganisms, such as enteric gram negative bacilli and Pseudomonas aeruginosa may be more frequent. Other studies have shown that the severity of the COPD is an important determinant of the type of microorganism. In patients with mild COPD, S. pneumoniae is predominant. When the FEV_1 is lower, H. influenzae and M. catarrhalis are more frequent and P. aeruginosa may appear in patients with a more severe degree of airways obstruction (see Stratification of Patients with COPD, below). The risk factors for P. aeruginosa infection are recent hospitalisation, frequent administration of antibiotics (4 courses in the last year), very severe COPD (Stage IV), and isolation of P. aeruginosa during a previous exacerbation or colonization during a stable period. Stratification of Patients with COPD Exacerbated for Antibiotic Treatment and Potential Microorganisms Involved in Each Group Group A: Patients not requiring hospitalization (Stage I: Mild COPD) Definition: Mild exacerbation Microorganisms: • H. influenzae • S. pneumonia • M. catarrhalis • Chlamydia pneumoniae* • Viruses Group B: Patients admitted to hospital (Stages II-IV: Moderate to Very Severe COPD) Definition: Moderate-severe exacerbation without risk factors for P. aeruginosa infection Microorganisms: • Group A microorganisms plus: • Enterobacteriaceae (K. pneumoniae, E. coli, Enterobacter, etc.) Group C: Patients admitted to hospital (Stages II-IV: Moderate to Very Severe COPD) Definition: Moderate-severe exacerbation with risk factors for P. aeruginosa infection

Microorganisms:

- Group B microorganisms plus:
- P. aeruginosa

Note for GROUP: In some settings, patients with moderate to severe exacerbations may be treated as outpatients. In this case, patients may best be stratified into two groups: an uncomplicated group without any risk factors and a complicated group that has one or more "risk factors" (comorbidity, severe COPD, frequent exacerbations, antimicrobial use within last 3 months). The uncomplicated group: use Group A recommendations in the table below. Complicated group: use Group B or C recommendations (oral treatment) in the table below.

Note for DEFINITION: severity refers to the exacerbation, though this is intertwined with the severity of the underlying COPD.

*Note: Chlamydia pneumonia (or Chlamidophila pneumoniae) has not been confirmed as a cause of exacerbation in some areas (e.g., UK).

There is no clear information about when to use oral or intravenous (IV) route of administration in hospitalized patients. The route of administration depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic. The oral route is preferred. Otherwise, the IV route has to be used, switching to oral when there is clinical stabilization. Antibiotic treatment in patients with exacerbations of COPD should be maintained for 3 to 10 days. See below for recommended antibiotic treatment in exacerbations of COPD.

Ten to thirty percent of COPD exacerbated patients do not respond to empiric antimicrobial treatment. In such cases the patient should be re-evaluated for complications that can aggravate symptoms and mimic exacerbations (e.g., cardiac failure, pulmonary embolism, non-compliance with prescribed medications); microbiological reassessment of these patients is recommended.

Antibiotic Treatment in Exacerbations of COPD[a,b]

Group A:

Oral Treatment (No particular order)

Patients with only one cardinal symptom should not receive antibiotics. If indication, then:

- Beta-lactam (Ampicillin/Amoxicillin[c])
- Tetracycline
- Trimethoprim/Sulfamethoxazole

	Alternative Treatment (No particular order) • Beta-lactam/Beta-lactamase inhibitor (Co-amoxiclav) • Macrolides (Azithromycin, Clarithromycin, Roxithromycin[d]) • Cephalosporins - 2nd or 3rd generation • Ketolides (Telithromycin) Parenteral Treatment (No particular order) • Not applicable Group B: Oral Treatment (No particular order) • Beta-lactam/ Beta-lactamase inhibitor (Co-amoxiclav) Alternative Treatment (No particular order) • Fluoroquinolones[d] (Gatifloxacin, Gemifloxacin, Levofloxacin, Moxifloxacin) Parenteral Treatment (No particular order) • Beta-lactam/ beta-lactamase inhibitor (Co-amoxiclav, ampicillin/sulbactam) • Cephalosporins - 2nd or 3rd generation • Fluoroquinolones[d] (Gatifloxacin, Levofloxacin, Moxifloxacin) Group C: Oral Treatment (No particular order) • Fluoroquinolones (Ciprofloxacin, Levofloxacin - high dose[e]) Alternative Treatment (No particular order) • Not applicable Parenteral Treatment (No particular order) • Fluoroquinolones (Ciprofloxacin, Levofloxacin - high dose[e]) or • Beta-lactam with P. aeruginosa activity Note[a] All patients with symptoms of a COPD exacerbation should be treated with additional bronchodilators + glucocorticosteroids. Note[b] Classes of antibiotics are provided (with specific agents in parentheses). In

	countries with high incidence of S. pneumoniae resistant to penicillin, high dosages of Amoxicillin or Co-Amoxiclav are recommended. (See "Stratification of Patients with COPD" above for definitions of Groups A, B, C.) Note[c] This antibiotic is not appropriate in areas where there is increased prevalence of beta-lactamase producing H. influenzae and M. catarrhalis, and/or of S. pneumoniae resistance to penicillin. Note[d] Not available in all areas of the world Note[e] Dose 750 mgs effective against P. aeruginosa
NCCCC / NICE (2004)	A - Antibiotics should be used to treat exacerbations of COPD associated with a history of more purulent sputum. B - Patients with exacerbations without more purulent sputum do not need antibiotic therapy unless there is consolidation on a chest radiograph or clinical signs of pneumonia. D - Initial empirical treatment should be an aminopenicillin, a macrolide, or a tetracycline. When initiating empirical antibiotic treatment, prescribers should always take account of any guidance issued by their local microbiologists. D - When sputum has been sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities when they become available.
NON-PHARMACOLOGIC TREATMENT	
Oxygen	
ACP / ACCP (2001)	Oxygen, with caution, in hypoxemic patients is a beneficial therapeutic option in the treatment of patients presenting to the hospital with moderate or severe acute exacerbations of COPD. Ample evidence shows that oxygen therapy provides important benefits to inpatients with acute exacerbations of COPD and hypoxemia. The major concern with the administration of this therapy is the risk for resultant hypercarbia and respiratory failure. In three observational studies, most patients with acute exacerbations of COPD developed hypercarbia after oxygen administration (FiO_2 ranged from 24% to 28%). These studies seem to suggest that the relationship between pH and PO_2 at presentation is a good predictor of the risk for hypercarbia and subsequent failure.
Finnish (2004)	Oxygen by nasal catheter or by venturi mask. Caution should be exercised when dosing (if the result of an arterial blood gas analysis is not available, the concentration of mask oxygen should not exceed 28%, or nasal catheter flow should not exceed

	more than 2 L/minutes in patients above 50 years of age).
GOLD (2005)	Hospital Management Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Adequate levels of oxygenation (PaO_2 >8.0 kPa, 60 mm Hg, or SaO_2 >90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks are more accurate sources of controlled oxygen than are nasal prongs but are more likely to be removed by the patient.
NCCCC/NICE (2004)	D - The oxygen saturation should be measured in patients with an exacerbation of COPD, if there are no facilities to measure arterial blood gases. C - If necessary, oxygen should be given to keep the SaO_2 greater than 90%. D - Pulse oximeters should be available to all healthcare professionals managing patients with exacerbations of COPD, and they should be trained in their use. Clinicians should be aware that pulse oximetry gives no information about the PCO_2 or pH. D - In the interim period while the recommendation on the availability of oximeters is implemented, oxygen should be given to all patients with an exacerbation of COPD who are breathless, if the oxygen saturations are not known. D - During the transfer to hospital the following points should be considered: • It is not desirable to exceed an oxygen saturation of 93%. Oxygen therapy should be commenced at approximately 40% and titrated upwards if saturation falls below 90% and downwards if the patient becomes drowsy or if the saturation exceeds 93-94%. • Patients with known type II respiratory failure need special care, especially if they require a long ambulance journey or if they are given oxygen at home for a prolonged period before the ambulance arrives. D - When the patient arrives at hospital, arterial blood gases should be measured and the inspired oxygen concentration noted in all patients with an exacerbation of COPD. Arterial blood gas measurements should be repeated regularly, according to the

	response to treatment. D - The aim of supplemental oxygen therapy in exacerbations of COPD is to maintain adequate levels of oxygenation (SaO_2 greater than 90%), without precipitating respiratory acidosis or worsening hypercapnia. Patients with pH <7.35 should be considered for ventilatory support.
Noninvasive and Invasive Ventilation	
ACP / ACCP (2001)	In the treatment of patients presenting to the hospital with moderate or severe acute exacerbation of COPD, NIPPV administered under the supervision of a trained physician is a beneficial therapeutic option. NIPPV is frequently used in the inpatient management of patients with acute exacerbations of COPD. It not only improves ventilation and decreases PCO_2 levels but, in many instances, is also a means of avoiding intubation. In five randomized, controlled trials and five observational studies, NIPPV was a beneficial support strategy and decreased the likelihood of respiratory failure requiring invasive mechanical ventilation. Some data show that NIPPV might improve survival of patients with acute exacerbations of COPD. These conclusions, however, are weakened by issues of study design, such as unclear selection criteria for patients receiving therapy, and the uncertain number of patients who were screened but excluded from the trials. Further studies are needed to provide information on which patients would benefit most from this intervention.
Finnish (2004)	Non-invasive ventilation has improved recovery in severe acute exacerbations of COPD (A).
GOLD (2005)	Hospital Management <u>NIPPV</u> NIPPV has been studied in many uncontrolled and five randomized controlled trials in acute respiratory failure. The studies show consistently positive results with success rates of 80-85%. Taken together they provide evidence that NIPPV increases pH, reduces $PaCO_2$, reduces the severity of breathlessness in the first 4 hours of treatment, and decreases the length of hospital stay (Evidence A). More importantly, mortality - or its surrogate, intubation rate - is reduced by this intervention. However, NIPPV is not appropriate for all patients. Selection and Exclusion Criteria for NIPPV:

Selection Criteria

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Moderate to severe acidosis (pH 7.35) and hypercapnia (Pa CO_2 >6.0 kPa, 45 mmHg)
- Respiratory frequency 25 breaths per minute

Exclusion Criteria (any may be present)

- Respiratory arrest
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- Somnolence, impaired mental status, uncooperative patient
- High aspiration risk; viscous or copious secretions
- Recent facial or gastroesophageal surgery
- Craniofacial trauma, fixed nasopharyngeal abnormalities
- Burns
- Extreme obesity

<u>Invasive Mechanical Ventilation</u>

Patients who show impending acute respiratory failure and those with life-threatening acid-base status abnormalities and/or altered mental status despite aggressive pharmacologic therapy are likely to be the best candidates for invasive (conventional) mechanical ventilation. The three ventilatory modes most widely used are assisted-control ventilation and pressure support ventilation alone or in combination with intermittent mandatory ventilation.

Indications for Invasive Mechanical Ventilation

- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Respiratory frequency >35 breaths per minute
- Life-threatening hypoxemia (PaO_2 <5.3 kPa, 40 mmHg or PaO_2/FiO_2* <200 mmHg)
- Severe acidosis (pH <7.25) and hypercapnia ($PaCO_2$ >8.0 kPa, 60 mmHg)
- Respiratory arrest
- Somnolence, impaired mental status
- Cardiovascular complications (hypotension, shock, heart failure)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)
- NIPPV failure (or exclusion criteria [see above])

* FiO_2: Fractional concentration of oxygen in dry inspired gas

NCCCC/NICE (2004)	Non-invasive Ventilation (NIV) and COPD Exacerbations A - NIV should be used as the treatment of choice for persistent hypercapnic ventilatory failure during exacerbations despite optimal medical therapy. D - It is recommended that NIV should be delivered in a dedicated setting with staff who have been trained in its application, who are experienced in its use, and who are aware of its limitations. D - When patients are started on NIV, there should be a clear plan covering what to do in the event of deterioration and ceilings of therapy should be agreed. Invasive Ventilation and Intensive Care C - Patients with exacerbations of COPD should receive treatment on intensive care units, including invasive ventilation when this is thought to be necessary. D - During exacerbations of COPD, functional status, body mass index (BMI), requirement for oxygen when stable, comorbidities, and previous admissions to intensive care units should be considered, in addition to age and FEV_1, when assessing suitability for intubation and ventilation. Neither age nor FEV_1 should be used in isolation when assessing suitability. A - NIV should be considered for patients who are slow to wean from invasive ventilation.
HOSPITAL DISCHARGE AND FOLLOW-UP	
Discharge Criteria	
ACP/ACCP (2001)	No recommendations offered.
Finnish (2004)	No recommendations offered
GOLD (2005)	Insufficient clinical data exist to establish the optimal duration of hospitalization for acute exacerbations of COPD. Consensus and limited data support the discharge criteria listed below: • Inhaled $beta_2$-agonst therapy is required no more frequently than every 4 hours. • Patient, if previously ambulatory, is able to walk across room.

	• Patient is able to eat and sleep without frequent awakening by dyspnea. • Patient has been clinically stable for 12 to 24 hours. • Arterial blood gases have been stable for 12 to 24 hours. • Patient (or home caregiver) fully understands correct use of medications. • Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions). • Patient, family, and physician are confident patient can manage successfully. Follow-up The following items should be included in a follow-up assessment 4 to 6 weeks after discharge from the hospital. • Ability to cope in usual environment • Measurement of FEV_1 • Reassessment of inhaler technique • Understanding of recommended treatment regimen • Need for long-term oxygen therapy and/or home nebulizer (for patients with very severe COPD) Thereafter, follow-up is the same as for stable COPD (see Part I of this synthesis), including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters. Home visits by a community nurse may permit earlier discharge of patients hospitalized with an exacerbation of COPD, without increasing readmission rate.
NCCCC/NICE (2004)	D - Spirometry should be measured in all patients before discharge. D - Patients should be re-established on their optimal maintenance bronchodilator therapy before discharge. D - Patients who have had an episode of respiratory failure should have satisfactory oximetry or arterial blood gas results before discharge. D - All aspects of the routine care that patients receive (including appropriateness and risk of side effects) should be assessed before discharge. D - Patients (or home carers) should be given appropriate information to enable them to fully understand the correct use of medications, including oxygen, before discharge.

	D - Arrangements for follow-up and home care (such as visiting nurse, oxygen delivery, referral for other support) should be made before discharge. D - Before the patient is discharged, the patient, family, and physician should be confident that he or she can manage successfully. When there is remaining doubt a formal activities of daily living assessment may be helpful.
Follow-up/Monitoring Recovery	
ACP/ACCP (2001)	No recommendations offered.
Finnish (2004)	No recommendations offered
GOLD (2005)	Items to include in a follow-up assessment 4 to 6 weeks after discharge from the hospital are listed below: • Ability to cope in usual environment • Measurement of FEV_1 • Reassessment of inhaler technique • Understanding of recommended treatment regimen • Need for long-term oxygen therapy and/or home nebulizer (for patients with severe COPD) Thereafter, follow-up is the same as for stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters. If hypoxemia developed during the exacerbation, arterial blood gases should be rechecked at discharge and at the follow-up visit. If the patient remains hypoxemic, long-term oxygen therapy should be instituted. Decisions about continuous domiciliary oxygen based on the severity of the acute hypoxemia during an exacerbation are frequently misleading.
NCCCC/NICE (2004)	D - Patient's recovery should be monitored by regular clinical assessment of their symptoms and observation of their functional capacity. D - Pulse oximetry should be used to monitor the recovery of patients with nonhypercapnic, nonacidotic respiratory failure. D - Intermittent arterial blood gas measurements should be used to monitor the recovery of patients with respiratory failure who are hypercapnic or acidotic, until they are stable.

	D - Daily monitoring of PEF or FEV_1 should not be performed routinely to monitor recovery from an exacerbation because the magnitude of changes is small compared with the variability of the measurement.

TABLE 3: BENEFITS AND HARMS	
Benefits	
ACP / ACCP (2001)	Overall • To improve the care that patients receive by identifying efficacious and inefficacious treatment strategies • To reduce the number and severity of annual exacerbations Specific • NIPPV is a beneficial support strategy that decreases risk for invasive mechanical ventilation and possibly improves survival in selected hospitalized patients with respiratory failure
Finnish (2004)	Appropriate management and treatment of COPD may help relieve patient symptoms, improve exercise capacity, improve lung function, reduce morbidity and mortality, improve quality of life, and reduce frequency and severity of exacerbations.

GOLD (2005)	Overall
	• COPD prevention
	• The goals of effective COPD management are to:
	  • Prevent disease progression
	  • Relieve symptoms
	  • Improve exercise tolerance
	  • Improve health status
	  • Prevent and treat complications
	  • Prevent and treat exacerbations
	  • Reduce mortality

NCCCC / NICE (2004)	• If adopted, these guideline recommendations should lead to better standards of care and thus better outcomes from chronic obstructive pulmonary disease. • The frequency of exacerbations should be reduced by appropriate use of inhaled corticosteroids and

	bronchodilators and vaccinations.
Harms	
ACP / ACCP (2001)	Bronchodilators. Adverse effects of bronchodilators vary. The side effects of ipratropium bromide are generally fewer and milder. Three randomized, controlled trials did not report any adverse effects with ipratropium bromide. Other effects include increased incidence of tremors and dry mouth and urinary retention when used in combination with albuterol. The adverse effects of albuterol include tremors, headache, nausea, vomiting, and palpitations. Adverse cardiovascular effects, such as changes in heart rate, blood pressure, and electrocardiography tracings, are also possible but rare. Adverse effects associated with theophylline include nausea, vomiting, headache, arrhythmias, and seizures. The effects are more significant among patients with higher levels of theophylline. Corticosteroids. Hyperglycemia was the most common adverse effect associated with systemic corticosteroids for acute exacerbation of COPD. In the Systemic Corticosteroids in Chronic Obstructive Pulmonary Disease Exacerbations (SCCOPE) trial, two thirds of hyperglycemic episodes requiring treatment occurred in patients who were known to have diabetes mellitus. Nearly all episodes occurred in the first 30 days. Oxygen Therapy. The major concern for most clinicians administering oxygen therapy to patients with acute exacerbations of COPD is that oxygen supplementation will lead to hypercarbia and subsequent respiratory failure.
Finnish (2004)	Not stated
GOLD (2005)	Beta$_2$-agonists. Stimulation of beta$_2$-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta$_2$-agonists, whatever the route of administration, and this limits the dose that can be tolerated. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting beta$_2$-agonists, but the clinical significance of these changes is

	doubtful. Despite the concerns raised some years ago, further detailed study has found no association between beta$_2$-agonist use and an accelerated loss of lung function or increased mortality in COPD. Anticholinergics. Anticholinergic drugs, such as ipratropium bromide, are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 micrograms a day as a dry powder, does not retard mucus clearance from the lungs. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation. Methylxanthines. Toxicity is dose-related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental). Oral Glucocorticosteroids. A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD. Invasive Mechanical Ventilation. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation.
NCCCC/NICE (2004)	• Particular caution needs to be taken with the use of theophylline in elderly patients because of differences in pharmacokinetics, the increased likelihood of comorbidities, and the use of other medications. • Clinicians should be aware of the potential risk of developing osteoporosis and other side effects in patients treated with high-dose inhaled corticosteroids (especially in the presence

	of other risk factors) and should discuss the risk with patients. • Patients should be warned about the risks of fire and explosion if they continue to smoke when prescribed oxygen. • The technology appraisal also notes that zanamivir should be used with caution in people with COPD because of risk of bronchospasm. If people with COPD are prescribed zanamivir they should be made aware of the risks and have a fast-acting bronchodilator available. • Care should be taken when using intravenous theophylline because of interactions with other drugs and potential toxicity if the patient has been on oral theophylline.

TABLE 4: EVIDENCE AND RECOMMENDATION RATING SCHEMES	
ACP / ACCP (2001)	Each retrieved study was evaluated for external validity and internal validity. Internal Validity Scale for Observational Studies Grade of Recommendation - Level of Evidence Prognosis A. 1a: Systematic review (with homogeneity) of inception cohort studies or a clinical practice guideline validated on a test set 1b: Individual inception cohort study with $\geq$80% follow-up 1c: All-or-none case series 2a: Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomized, controlled trials B. 2b: Retrospective cohort study or follow-up of untreated control patients in a randomized, controlled trial, or clinical practice guideline not validated in a test set 2c / 3: "Outcomes" research

	C. 4: Case series (and poor-quality prognostic cohort studies) D. 5: Expert opinion without explicit critical appraisal, or expert opinion based on physiology, bench research, or "first principles" Diagnostic A. 1a: Systematic review (with homogeneity) of diagnostic studies or a clinical practice guideline validated on a test set 1b: Independent blinded comparison of an appropriate spectrum of consecutive patients, all of whom have undergone both the diagnostic test and the reference standard 1c: Diagnostic whose specificity is so high that a positive result rules in the diagnosis or a diagnostic finding whose sensitivity is so high that a negative result rules out the diagnosis (Absolute SpPins and SnNouts) 2a: Systematic review (with homogeneity) of studies with an internal validity score $\geq$2 B. 2b: Independent blinded comparison in nonconsecutive patients or confined to a narrow spectrum of study patients (or both), all of whom have undergone both the diagnostic test and the reference standard, or a diagnostic clinical practice guideline not validated in a test set 2c/3: Independent blinded comparison of an appropriate spectrum in which the reference standard was not applied to all study patients C. 4: Reference standard was not applied independently or was not applied blindly. D. 5: Expert opinion without explicit critical appraisal, or expert

	opinion based on physiology, bench research, or "first principles" Internal Validity of Experimental Studies: Internal validity of experimental studies was evaluated using the scoring system of Jadad, et al, 1996 (Jadad, AR, Moore, RA, Carroll, D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17[1]:1-12). Scores range from 0 to 5 and points are earned for adequate randomization, blinding, and assessment of withdrawals and dropouts. From: Bach PB, Brown C, Gelfand SE, McCrory DC. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001 Apr 3;134(7):600-20.
Finnish (2004)	Levels of Evidence A. Strong research-based evidence. Multiple relevant, high-quality scientific studies with homogeneous results. B. Moderate research-based evidence. At least one relevant, high-quality study or multiple adequate studies. C. Limited research-based evidence. At least one adequate scientific study. D. No research-based evidence. Expert panel evaluation of other information.
GOLD (2005)	Levels of Evidence A. Randomized controlled trials. Rich body of data. Definition: Evidence is from endpoints of well-designed randomized controlled trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants. B. Randomized controlled trials. Limited data. Definition: Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of randomized controlled trials, or meta-analysis of randomized controlled trials. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent. C. Nonrandomized trials. Observational studies. Definition: Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies. D. Panel consensus. Judgment. Definition: This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed

	insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.
NCCCC/NICE (2004)	Levels of Evidence Ia: Evidence from systematic reviews or meta-analysis of randomised controlled trials Ib: Evidence from at least one randomised controlled trial IIa: Evidence from at least one controlled study without randomisation IIb: Evidence from at least one other type of quasi-experimental study III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies IV: Evidence from expert committee reports or opinions and/or clinical experience of respected authorities NICE: Evidence from NICE guidelines or Health Technology Appraisal Programme HSC: Evidence from Health Service Circulars Grading of Recommendations Grade A: Based on hierarchy I evidence Grade B: Based on hierarchy II evidence or extrapolated from hierarchy I evidence Grade C: Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence Grade D: Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II, or III evidence

(ACP/ACCP), the Finnish Medical Society Duodecim (Finnish), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (a collaborative project of the World Health Organization and the National Heart, Lung, and Blood Institute), and the National Collaborating Centre for Chronic Conditions (a collaborating center for the National Institute for Health and Clinical Excellence [NCCCC/NICE]) present recommendations for management of acute exacerbations of COPD and provide explicit reasoning behind their judgments. Finnish, GOLD, and NCCCC/NICE identify the type of supporting evidence for selected recommendations. Although ACP/ACCP does not specifically state the type of supporting evidence for individual recommendations, they mention in their guideline that their recommendations are based on the highest quality evidence available at the time. They further note that, while studies of highest quality were often randomized controlled clinical trials, these were few in number and tended to enroll small numbers of patients

As mentioned above in the introduction, the scope and format of the guidelines vary. While Finnish, GOLD, and NCCCC/NICE address both management of stable COPD and acute exacerbation, the ACP/ACCP guideline applies only to acute exacerbations of COPD in the emergency department or inpatient setting. The ACP/ACCP guideline presents the available evidence on risk stratification for relapse and 6-month mortality rates, diagnostic testing for acute exacerbations of COPD, and current treatment options (both pharmacologic and non-pharmacologic) for acute exacerbations.

The GOLD guideline differs from the other guidelines in its global perspective and in its emphasis on prevention strategies. This guideline presents a COPD management plan with four components: (1) assessment and monitoring of disease, (2) reduction of risk factors, (3) management of stable COPD, and (4) management of exacerbations. The GOLD guideline also differs from the other two guidelines in including recommendations for pulmonary rehabilitation and surgical treatment of COPD.

The NCCCC/NICE guideline, like the GOLD guideline, is broad in scope, extensively covering the diagnosis and management of both chronic and acute exacerbation of COPD. This guideline also includes discussion of the evidence (and recommendations) related to the use of respiratory stimulants and respiratory physiotherapy for exacerbations of COPD.

Both the GOLD and NCCCC/NICE guidelines differ from the Finnish and the ACP/ACCP guidelines by including recommendations for pulmonary rehabilitation which are addressed in Part III of this synthesis (currently under development).

Areas of Agreement

Signs and Symptoms of Acute Exacerbation

Although there is some difference among the guidelines in the specific symptoms noted for acute exacerbation of COPD, all groups recognize worsening dyspnea, increase in sputum purulence, and increase in sputum volume as cardinal symptoms of acute exacerbation.

Chest X-ray and ECG

ACP/ACCP, GOLD, and NCCCC/NICE recommend chest x-ray in the initial evaluation of patients with suspected acute exacerbation. Both GOLD and NCCCC/NICE also recommend ECG. Finnish does not offer recommendations for either chest x-ray or ECG; ACP/ACCP does not offer recommendations for ECG.

Measurement of Arterial Blood Gases

ACP/ACCP, GOLD, and NCCCC/NICE agree that arterial blood gas analysis is important both to assess severity of acute exacerbations and to gauge the need for oxygen therapy or ventilatory support. Finnish does not offer recommendations.

Indications for Hospital Management

Both GOLD and NCCCC/NICE agree that certain patients require hospitalization and/or even, according to GOLD, admission to ICUs. The specific criteria for hospital admission vary, although generally, they agree that hospitalization is necessary for a marked increase in intensity of symptoms. NCCCC/NICE discusses hospital-at-home and assisted discharge schemes as an alternative way of managing patients with exacerbations of COPD who would otherwise need to be admitted or stay in the hospital.

Short-acting $Beta_2$-Agonists and/or Inhaled Anticholinergics

ACP/ACCP, Finnish, and GOLD all recommend short-acting $beta_2$ agonists as pharmacologic management of acute exacerbations. NCCCC/NICE acknowledges use of short-acting bronchodilators without specifying type. ACP/ACCP recommends inhaled short-acting $beta_2$ agonists secondary to inhaled anticholinergics (see areas of disagreement).

ACP/ACCP, Finnish, and GOLD recommend combination therapy with inhaled anticholinergic and short-acting $beta_2$ agonists if a patient fails to respond to initial single-agent therapy. GOLD acknowledge that the evidence for the effectiveness of this combination remains controversial.

Methylxanthines

The guidelines are in general agreement that methylxanthines (theophylline, aminophylline) cannot be routinely recommended in patients with acute exacerbation of COPD because of their potential toxicity. Finnish, GOLD and NCCCC/NICE however note that they may be used as an adjunct to other therapies when response to other treatments is poor. Monitoring of serum theophylline levels is recommended if clinicians choose to use these agents.

Use of Systemic Corticosteroids

All of the guidelines agree that systemic corticosteroids are beneficial in hospitalized patients with acute exacerbation. All organizations provide guidance on duration of steroid treatment. ACP/ACCP states that systemic corticosteroids can be given for up to two weeks in patients who are not receiving long-term therapy with oral steroids. Finnish and NCCCC/NICE recommend oral

corticosteroids for 7 to 14 days. GOLD states that a 10- to 14-day course of oral prednisolone is reasonable. GOLD also recommends systemic steroids for outpatient management. Steroids should be given in addition to bronchodilator therapy.

Use of Antibiotics

There is general agreement among all four guidelines that antibiotics are beneficial in patients with severe exacerbation (i.e. those with increased sputum volume and purulence). Benefits of antibiotics are less clear in patients without severe exacerbation. ACP/ACCP recommends use of older antibiotics such as amoxicillin, trimethoprim-sulfamethoxazole, and tetracyclines for treatment. Finnish states that antimicrobial treatment in exacerbation of COPD is controversial; however, when antibiotics are deemed necessary, they recommend amoxicillin, doxycycline, or sulpha-trimethoprim. GOLD states that the choice of antibiotic should be based on the severity of the exacerbation, which is an important determinant of the type of microorganism present. In general, GOLD recommends oral treatment with beta-lactams (ampicillin/amoxicillin), tetracycline, or trimethoprim/sulfamethoxazole for mild exacerbations, beta-lactam/beta-lactamase inhibitor for moderate-severe exacerbations without risk factors for Pseudomonas aeruginosa infection, and fluoroquinolones (ciprofloxacin, levofloxacin - high dose) for moderate-severe exacerbations with risk factors for P. aeruginosa infection. GOLD provides additional recommendations for alternative regimens (particularly for areas with high incidence of S. pneumoniae resistant to penicillin) and parental treatment. NCCCC/NICE recommends initial empirical treatment with an aminopenicillin, a macrolide, or a tetracycline. In addition, NCCCC/NICE cautions that when initiating empirical antibiotic treatment, prescribers should always take account of any guidance issued by their local microbiologists. When sputum has been sent for culture, the appropriateness of antibiotic treatment should be checked against laboratory culture and sensitivities when they become available.

Oxygen Therapy

The guidelines are unanimous in their recommendations for oxygen therapy in all patients with acute exacerbation and hypoxemia. They also recommend blood gas monitoring to guard against hypercarbia and subsequent respiratory failure.

Mechanical Ventilation

All of the guidelines agree that noninvasive mechanical ventilation is a beneficial therapeutic option for patients with severe exacerbations to prevent respiratory failure. Use of noninvasive methods can reduce the need for intubation. GOLD also provides explicit indications for the use of invasive mechanical ventilation.

Discharge Criteria

GOLD and NCCCC/NICE are in general agreement on the discharge criteria for patients with acute exacerbation of COPD. These include stability of the patient's condition, need for bronchodilators not more frequent than every 4 hours or the re-establishment of optimal maintenance bronchodilator therapy before discharge, and follow-up and home care arrangements completed. ACP/ACCP and Finnish do

not offer any recommendations regarding discharge criteria for patients with acute exacerbation of COPD.

Areas of Differences

Measurement of Airflow Limitation - Spirometry

Guidelines differ in their recommendations for use of spirometry in diagnosing acute exacerbation. ACP/ACCP states that spirometry should not be used to diagnose an exacerbation or to assess its severity. This recommendation is based on observational studies showing that spirometry performed at presentation or during treatment was not useful in judging severity or guiding management of patients during acute exacerbation. Furthermore, they report that FEV_1 has shown no significant correlation with PO_2 and only a weak correlation with PCO_2. NCCCC/NICE states that changes in lung function at the time of an exacerbation are usually small and are not helpful in routine practice. However, in certain situations, investigations may assist in ensuring appropriate treatment is given, particularly when the patient presents for the first time during an exacerbation. GOLD, on the other hand, states that spirometry can be useful in diagnosing acute exacerbation, particularly when values are compared with prior measurements of lung function, as an acute change in these tests is more important than their absolute values. Nevertheless, GOLD acknowledges that even simple lung function tests can be difficult for sick patients. Finnish does not offer specific recommendations for spirometry in acute exacerbations.

Use of Bronchodilators

There is some disagreement among the guidelines on the choice of first-line bronchodilators for patients with acute exacerbation. ACP/ACCP, Finnish, and GOLD all agree that both short-acting $beta_2$-agonists and anticholinergics are effective bronchodilators; however, ACP/ACCP recommends that inhaled anticholinergics be used first because of their more benign side effect profile. GOLD, on the other hand, recommends short-acting inhaled $beta_2$ agonists as primary therapy for hospital management. NCCC/NICE does not offer specific recommendations for the use of bronchodilating agents during an acute exacerbation of COPD.

This Synthesis was prepared by ECRI on October 8, 2001. It was reviewed by the guideline developers as of November 15, 2001. It was updated to include NCCCC/NICE and Finnish, and updated GOLD recommendations, on March 24, 2005. The information was verified by NICE on May 3, 2005. This Synthesis was updated on October 20, 2005 to reflect updated GOLD guidelines.

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